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Fused Pyrimidines. I. A One-step Synthesis of 3-Aminoisothiazolo[3,4-*d*]-pyrimidines from 6-Aminouracils and Vilsmeier Reagents

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Reaction of 6-amino-1,3-diethyluracil (Ib) with dimethylformamide–thionyl chloride afforded 5,7-diethyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H, 7H)-dione (IVb) and three minor products (VIb, VIIb, VIIIb). Similar reactions of five 6-aminouracils or 6-amino-1-benzyl-cytosine (XV) with N-formyl-*sec*-amine–thionyl chloride afforded corresponding 3-aminoisothiazolo[3,4-*d*]pyrimidine derivatives (IVa—i or XVI). When 6-amino-1,3-diethyl-2-thiouracil (Ij) was allowed to react similarly, IVb was obtained as a major product and the yield of the expected 5,7-diethyl-3-dimethylaminoisothiazolo-[3,4-*d*]pyrimidin-4(5H)-one-6(7H)-thione (IVj) was very low.

During the course of our study directed toward the syntheses of fused pyrimidines having inhibitory activities against cyclic nucleotide phosphodiesterase, we have found a novel synthetic method of 3-aminoisothiazolo[3,4-*d*]pyrimidines (IV).

Reaction of 6-amino-1-ethyluracil (Ia)[2] with dimethylformamide (DMF)–thionyl chloride in chloroform for 1 hr under reflux, followed by treatment with water, afforded 6-amino-1-ethyl-5-formyluracil (IIIa). When the reaction time was changed to 20 hr, a side product was isolated in 9% yield. The elemental analysis ($C_9H_{12}O_2N_4S$), the nuclear magnetic resonance (NMR) spectrum (two N-methyl protons at δ 3.33 as well as one ethyl protons) and the ultraviolet (UV) spectrum (λ_{max}^{EtOH} nm: 233, 276, 305, Fig. 1) of the compound suggested two possible structures (IVa and Va). We presumed the compound to be 3-dimethylamino-7-ethylisothiazolo[3,4-*d*]pyrimidin-4,6(5H, 7H)dione (IVa), because the short time reaction

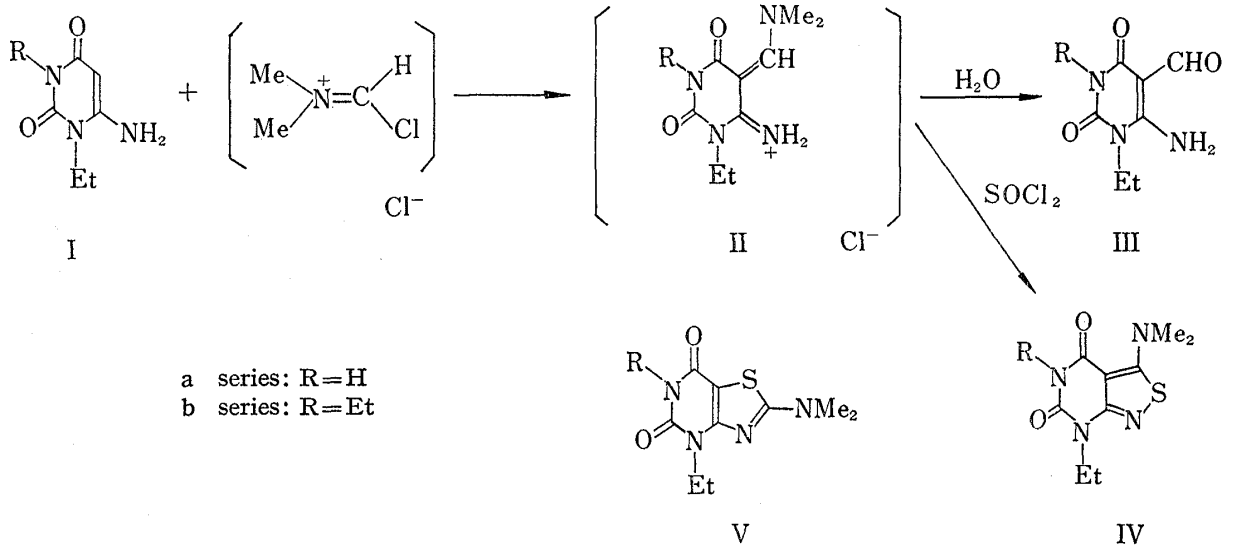


Chart 1

1) Location: *17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka.*
2) *a)* V. Papesch and E.F. Schroeder, *J. Org. Chem.*, **16**, 1879 (1951); *b)* H. Bredereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, **97**, 1403 (1964).

afforded IIIa exclusively, indicating that IIa was the first intermediate.[2b] The cyclization of IIa with thionyl chloride will first give the S-oxide of IVa rather than Va and subsequent deoxygenation will afford IVa, although the mechanism of the deoxygenation is not clear (Chart 1). It has been reported that cyclization through sulfur between carbon-carbon,[3] carbon-nitrogen,[4] and nitrogen-nitrogen[5] could be effected by thionyl chloride.

After several attempts to raise the yield of IV, Ib was refluxed with one equivalent of DMF and excess thionyl chloride in 1,2-dichloroethane for 5.5 hr. The reaction product was chromatographed on silica gel to afford four compounds, A, B, C and D, in yields of 43%, 6%, 23% and 5%, respectively. Compound A had the same UV spectrum as that of IVa and was assigned the structure 5,7-diethyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidin-4,6[5H,7H]-dione (IVb) on the basis of its elemental analysis ($C_{11}H_{16}O_2N_4S$), mass spectrum (M^+=268) and NMR spectrum (two N-methyl protons at δ 3.37 as well as two ethyl protons). Desulfurization of IVb with Raney nickel afforded 6-amino-1,3-diethyl-5-methyluracil (IX), which excluded the possibility of the thiazolo[5,4-*d*]pyrimidine structure (Vb). Compound B was assigned the structure 5,7-diethyl-3-methylaminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H,7H)-dione (VIb)

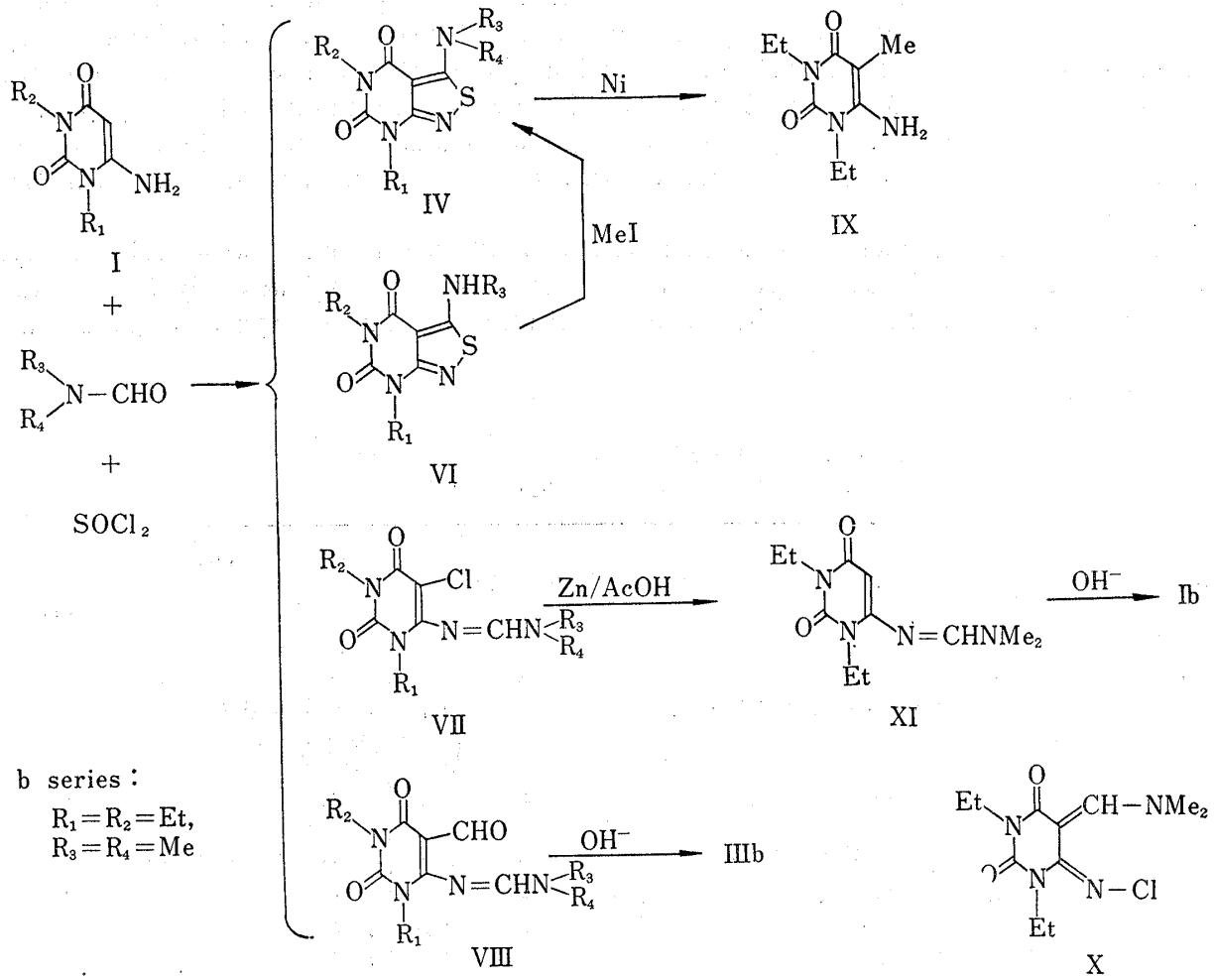


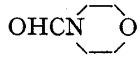
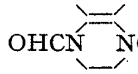
Chart 2

3) I.M. Goldman, *J. Org. Chem.*, **34**, 3285 (1969).
4) C.D. Hurd and R.I. Mori, *J. Am. Chem. Soc.*, **77**, 5359 (1955); T. Naito, S. Nakagawa, J. Okumura, K. Takahashi, and K. Kasai, *Bull. Chem. Soc. Japan*, **41**, 959 (1968); M. Davis and A.W. White, *J. Org. Chem.*, **34**, 2985 (1969); M. Davis, T.G. Paproth, and L.J. Stephens, *J. Chem. Soc.*, Perkin I, **1973**, 2057; Y. Mizuno, Y. Watanabe, and K. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **22**, 1198 (1974).
5) F.F. Blicke and H.C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 798 (1954).

on the basis of its elemental analysis ($C_{10}H_{14}O_2N_4S$), NMR spectrum [one N-methyl protons (doublet) at δ 2.92 as well as two ethyl protons] and the formation of IVb on methylation with methyl iodide. When the reaction time was increased three-fold (16.5 hr), the yield of IVb decreased to 30% whereas the yield of VIb increased to 15%, indicating that the de-methylation of IVb to VIb took place under the above conditions. Two structures (VIIb and X) were possible for compound C on the basis of its elemental analysis ($C_{11}H_{17}O_2N_4Cl$) and NMR spectrum (two N-methyl protons at δ 3.13 and 3.18, one vinyl proton at δ 7.85 as well as two ethyl protons). Compound C was resistant to catalytic reduction over Raney nickel but was de-chlorinated by heating it with zinc–acetic acid to afford 1,3-diethyl-6-(dimethylaminomethylene)aminouracil (XI), whose structural assignment was based on its elemental analysis, NMR spectrum and the formation of Ib upon alkaline hydrolysis. Accordingly, compound C was assigned the structure 5-chloro-1,3-diethyl-6-(dimethylaminomethylene)aminouracil (VIIb) rather than X. Compound D was assigned the structure 1,3-diethyl-6-(dimethylaminomethylene)amino-5-formyluracil (VIIIb) on the basis of its elemental analysis, NMR spectrum and the formation of IIIb upon alkaline hydrolysis (Chart 2). Similar reactions of 6-aminouracils (Ic—i), thionyl chloride and various N-formyl-*sec*-amine such as N,O,O′-triformyldiethanolamine, N-formylmorpholine,[6] N,N′-diformylpiperazine[7] and diethylformamide in 1,2-dichloroethane or methylene chloride afforded corresponding isothiazolo[3,4-*d*]-pyrimidines (IVc—i) (Table I). When N,O,O′-triformyldiethanolamine was used, a part of the O-formyl groups was removed during the reaction and the resultant hydroxyl group was chlorinated to afford IVc′. Isolation of minor products was not attempted except VII in series d, f, h. Properties of the compounds described above are summarized in Tables II, III, Figs. 1 and 2.

When 6-amino-1,3-diethyl-2-thiouracil (Ij) was allowed to react with DMF–thionyl chloride in dichloromethane, the yield of the expected 6-thione (IVj) was only 7% and the main product was IVb, the mechanism of the substitution of sulfur by oxygen being unknown (Chart 3).

Table I. The Reaction of 6-Aminouracils (I) and N-Formyl-*sec*-amine–Thionyl Chloride

Series	I[a]	N-Formylamine	Solvent[b]	Method[c]	IV	Yield (%) IV	Yield (%) VII
b	$R_1=R_2=Et$	DMF	E	A	$R_3=R_4=Me$	43	23
c	$R_1=R_2=Et$	$OHCN(CH_2CH_2OCHO)_2$	E	A	$R_3=R_4=CH_2CH_2OH$	34	
c′					$R_3=CH_2CH_2OH$, $R_4=CH_2CH_2Cl$	11	
d	$R_1=R_2=Et$		E	A		42	24
e	$R_1=R_2=Bu$		E	A		19	
f	$R_1=R_2=Et$	$OHCNEt_2$	M	A	$R_3=R_4=Et$	54	19
g	$R_1=iBu$, $R_2=H$	DMF	M	C	$R_3=R_4=Me$	59	
h	$R_1=CH_2CH_2OMe$, $R_2=H$	DMF	M	C	$R_3=R_4=Me$	54	4
i	$R_1=R_2=Me$	DMF	M	C	$R_3=R_4=Me$	48	

a) Et, ethyl; Bu, butyl; iBu, iso-butyl; Me, methyl
b) E, 1,2-dichloroethane; M, dichloromethane
c) A, silica gel chromatography; C, direct crystallization; see Experimental

6) L. Médard, *Bull. Soc. Chim. France* [5], **3**, 1343 (1936).
7) J.H. Robson and J. Reinhart, *J. Am. Chem. Soc.*, **77**, 2453 (1955).

TABLE II. 3-(Substd.)aminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H,7H)-diones (IV)

Compd.	mp[a] (°C)	UV λ_{max}^{EtOH} (nm)	Formula	Analysis (%) Found (Calcd.) C	H	N	S	NMR Solvent	NMR δ (ppm)
IVa	222—223	233, 276, 305	$C_9H_{12}O_2N_4S$	44.67 (44.99)	4.68 (5.03)	23.23 (23.32)	13.13 (13.34)	d_6-DMSO	1.19 (3H, t), 3.33 (6H, s), 3.97 (2H, q), 10.8 (1H)
IVb	88—90	235, 278, 308	$C_{11}H_{16}O_2N_4S$	49.24 (49.23)	5.89 (6.01)	20.91 (20.88)	11.73 (11.95)	$CDCl_3$	1.20, 1.29 (3H, t), 3.37 (6H, s), 4.04, 4.16 (2H, q)
IVc	85—87	239, 280, 314	$C_{13}H_{20}O_4N_4S$	47.48 (47.54)	6.19 (6.14)	16.97 (17.06)	9.76 (9.77)	$CDCl_3$	1.27, 1.35 (3H, t), 3.5—4.4 (14H)
IVc′	88—90	238, 280, 313	$C_{13}H_{19}O_3N_4SCl$[b]	44.95 (45.01)	5.40 (5.52)	15.96 (16.15)	10.57 (9.25)	$CDCl_3$	1.27, 1.35 (3H, t), 3.40 (1H), 3.6—4.3 (12H)
IVd	128—130	233, 284, 312	$C_{13}H_{18}O_3N_4S$	50.31 (50.30)	5.79 (5.84)	18.28 (18.05)	10.63 (10.33)	$CDCl_3$	1.23, 1.33 (3H, t), 3.6—4.4 (12H)
IVe	195—205	215, 282, 316	$C_{18}H_{27}O_3N_5S$	55.37 (54.95)	6.76 (6.92)	17.02 (17.78)	8.52 (8.15)		
IVf	75—76	239, 278, 313	$C_{13}H_{20}O_3N_4S$	52.39 (52.70)	6.75 (6.80)	18.95 (18.88)	10.74 (10.82)	CCl_4	0.9—1.5 (12H) 3.4—4.2 (8H)
IVg	199—200	233, 277, 306	$C_{11}H_{16}O_2N_4S$	49.24 (49.23)	6.05 (6.01)	21.06 (20.88)	11.88 (11.95)	$CDCl_3$	0.95 (6H, d), 2.1—2.6 (1H, m), 3.37 (6H, s) 3.92 (2H, d)
IVh	174—176	234, 277, 306	$C_{10}H_{14}O_3N_4S$	44.15 (44.43)	4.80 (5.22)	21.11 (20.73)	11.80 (11.86)	$CDCl_3$	3.5 (9H, s), 3.8, 4.4 (2H, t), 9.4 (1H)
IVi	150—152	234, 277, 307	$C_9H_{12}O_2N_4S$	44.89 (45.05)	4.79 (5.04)	23.32 (23.32)	13.36 (13.36)		

a) recrystallization solvent: b, d, g, h, i, MeOH; c, EtOH–ether; a, c′, e, EtOH; f, hexane
b) Cl, 10.57 (10.22)

TABLE III. 5-Chloro-6-(dimethylaminomethylene)aminouracils (VII)

Compd.	mp[a] (°C)	UV λ_{max}^{EtOH} (nm)	Formula	Analysis (%) Found (Calcd.) C	H	N	Cl	NMR Solvent	NMR δ (ppm)
VIIb	149	235, 255(s), 310	$C_{11}H_{17}O_2N_4Cl$	48.41 (48.45)	6.28 (6.28)	20.41 (20.53)	13.05 (13.00)	$CDCl_3$	1.20, 1.22 (3H, t), 4.10 (4H, q), 3.13, 3.18 (3H, s), 7.85 (1H, s)
VIId	153—154	235, 257, 310	$C_{13}H_{19}O_3N_4Cl$	49.69 (49.60)	5.99 (6.08)	17.82 (17.80)	11.26 (11.27)	$CDCl_3$	1.18, 1.20 (3H, t), 3.5—4.3 (12H), 7.92 (1H, s)
VIIf	syrup	234, 255(s), 310	$C_{13}H_{21}O_2N_4Cl$					d_6-DMSO	0.7—1.5 (12H), 2.9—4.2 (8H), 8.0 (1H, s)
VIIh	176—178	236, 263(s), 309	$C_{10}H_{15}O_3N_4Cl$	43.63 (43.72)	5.49 (5.50)	20.22 (20.40)	12.70 (12.90)	$CDCl_3$	3.26, 3.36 (3H, s), 3.5 (3H, s), 3.7, 4.26 (2H, t), 8.1 (1H, s), 11.4 (1H)

a) recrystallization solvent: MeOH

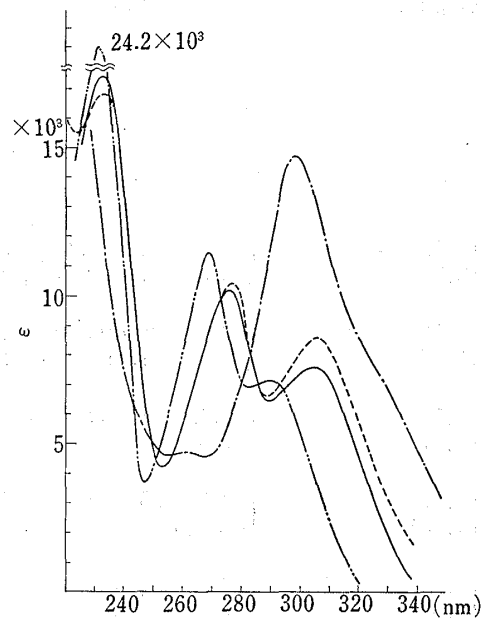


Fig. 1. UV Spectra of Some Typical Derivatives of Isothiazolo[3,4-*d*]-pyrimidine (in EtOH)

IVa: ——, IVl: ---- , VIb: —··—, XVI: ·—·—

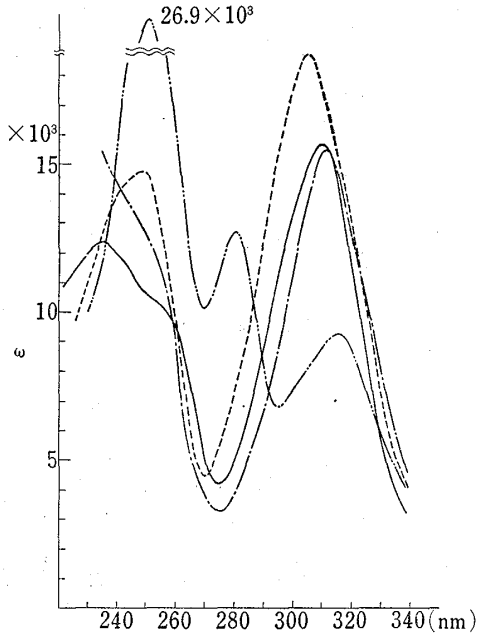
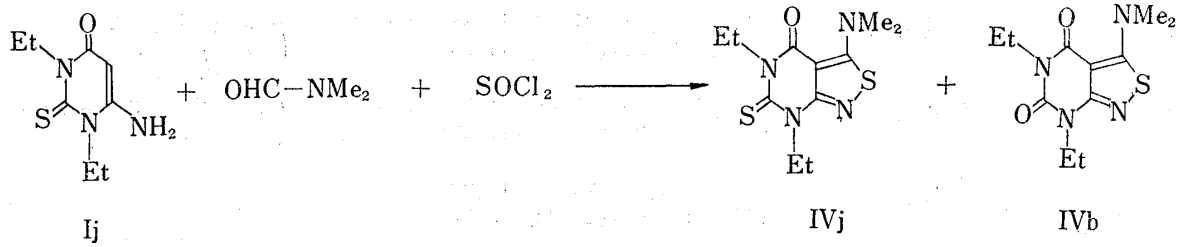


Fig. 2. UV Spectra of Some Typical Derivatives of Pyrimidine (in EtOH)

VIIb: ——, VIIIb: —·· —, XI: ------, XVII: ·—·—



Ij IVj IVb

Chart 3

Attempts were then made to apply the above reaction to 6-aminocytosines. Treatment of 6-amino-1-methylcytosine[8] (XII) with N-formylmorpholine–thionyl chloride in 1,2-dichloroethane did not afford the expected product, probably due to slight solubility of XII in the solvent. In order to overcome this difficulty, 6-amino-1-benzylcytosine (XV) was synthesized by the following route. 6-Amino-1-benzyluracil (Ik) was thiated with phosphorus pentasulfide in pyridine[9] to afford 6-amino-1-benzyl-4-thiouracil (XIII). Methylation of XIII with methyl iodide and treatment of the resulting S-methyl derivative with methanolic ammonia afforded XV.

Reaction of XV with DMF–thionyl chloride in 1,2-dichloroethane and silica gel chromatography of the reaction product afforded 4-amino-7-benzyl-3-dimethylaminoisothiazolo[3,4-*d*]-pyrimidin-6(7H)-one (XVI) and 1-benzyl-5-chloro-6-(dimethylaminomethylene)aminocytosine (XVII), whose structural assignments were based on their elemental analyses, UV and NMR spectra. For further confirmation of the structures, XVI and XVII were deaminated with sodium nitrite in acetic acid to afford 7-benzyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H,7H)-dione (IVl) and 1-benzyl-5-chloro-6-(dimethylaminomethylene)aminouracil (VIIl), respectively, which excluded the possibility of the structures XVIII and XIX (Chart 4), respectively.

8) W. Pfleiderer and H. Fink, *Chem. Ber.*, **96**, 2590 (1963).
9) T. Ueda, T. Tsuji, and H. Momoda, *Chem. Pharm. Bull.* (Tokyo), **11**, 912 (1963).

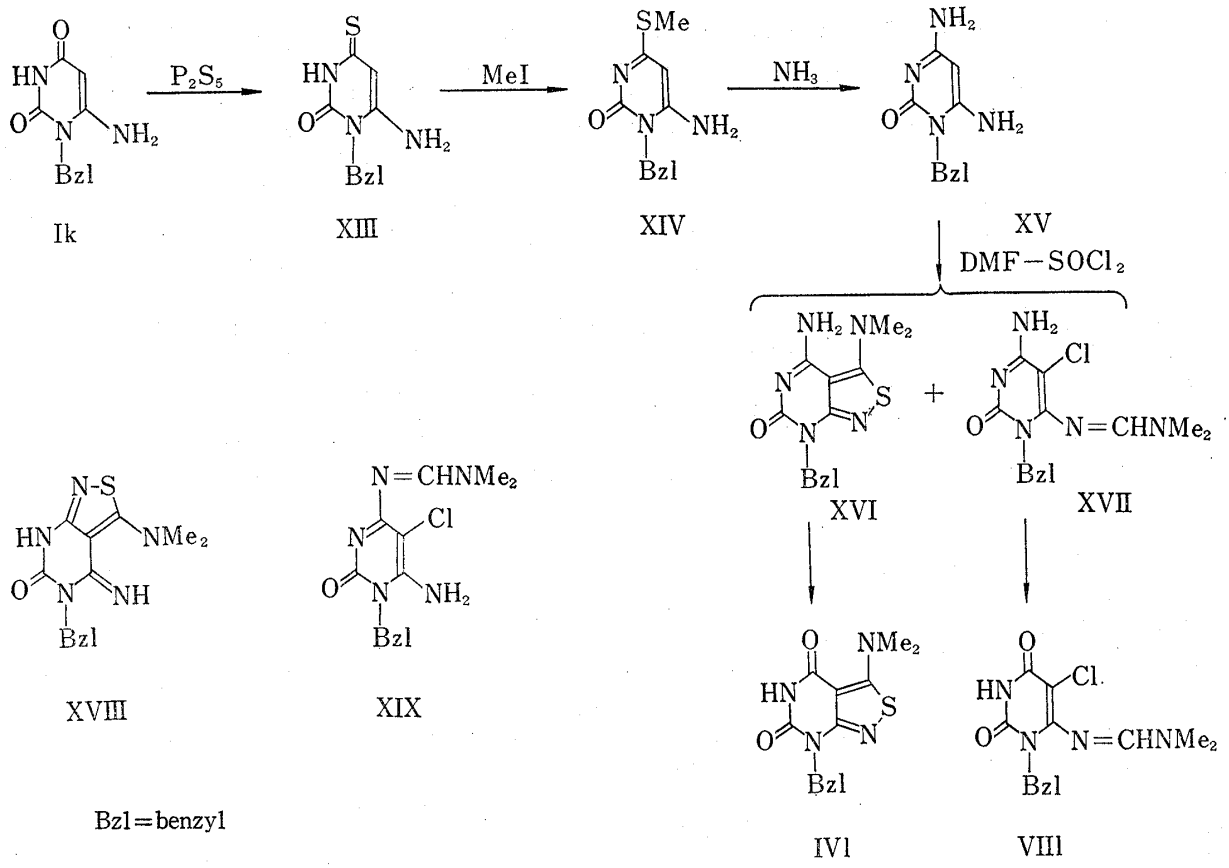


Chart 4

As to the synthesis of isothiazolo[3,4-*d*]pyrimidines, only one report has been published in which 3-alkyl derivatives were synthesized *via* 3-alkylisothiazoles.[10] Thus, we have found a novel method for the syntheses of 3-aminoisothiazolo[3,4-*d*]pyrimidines from 1-substituted-6-aminouracils and 1-benzyl-6-aminocytosine. Almost all isothiazolo[3,4-*d*]pyrimidines described above were more active than theophylline in inhibiting cyclic nucleotide phosphodiesterase, and the results will be published elsewhere.

Experimental[12]

6-Amino-1-ethyl-5-formyluracil (IIIa)——To an ice-cooled mixture of $CHCl_3$ (100 ml) and $SOCl_2$ (4.5 ml) was added DMF (2.36 g, 32.3 mmoles). After 30 min at 0°, Ia (5 g, 32.3 mmoles) was added and the mixture refluxed for 1 hr. The solution was evaporated to dryness *in vacuo* and the residue stirred with 5% aq. $NaHCO_3$ (50 ml). The precipitate was recrystallized from EtOH to afford colorless prisms (4.4 g, 75%), mp 295—300° (decomp.); UV λ_{max}^{EtOH} nm: 243, 283. *Anal.* Calcd. for $C_7H_9O_3N_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.54; H, 4.98; N, 22.74. NMR (d_6-DMSO) δ: 1.15 (3H, t, CH_3), 3.89 (2H, q, CH_2), 8.70 (1H, s, CHO), 8.5, 10.2, 10.9 (1H each, NH).

3-Dimethylamino-7-ethylisothiazolo[3,4-*d*]pyrimidin-4,6(5H, 7H)-dione (IVa)——The same reaction mixture as above was refluxed for 20 hr. The solution was evaporated to dryness *in vacuo* and the residue shaken with $CHCl_3$ and 5% aq. $NaHCO_3$ (50 ml each). The insoluble matter was filtered off and the $CHCl_3$ layer washed twice with H_2O. The $CHCl_3$ layer was evaporated to dryness *in vacuo*, and the residue recrystallized from EtOH to afford colorless needles (0.7 g, 9%).

10) K. Hartke and L. Peskar, *Arch. Pharmazie*, **301**, 611 (1968); When we were writing this paper, another report was published.[11]
11) R. Niess and H. Eilingsfeld, *Ann. Chem.*, **1974**, 2019.
12) Melting points were taken on a Yanaco micro melting point apparatus and are uncorrected. NMR spectra were recorded on a Hitachi R-24 spectrometer at 60 MHz using tetramethylsilane as an external reference. Thin-layer chromatography (TLC) was carried out on Merck aluminum sheets Silica gel F_{254}.

Reaction of 6-Amino-1,3-diethyluracil (Ib) with DMF-$SOCl_2$——A) To an ice-cooled mixture of 1,2-dichloroethane (20 ml) and $SOCl_2$ (10 ml) was added DMF (0.42 ml, 5.5 mmoles). After 15 min at 0°, Ib (1.01 g, 5.5 mmoles) was added and the mixture refluxed for 5.5 hr. The solution was evaporated to dryness *in vacuo* and the residue shaken with $CHCl_3$ (100 ml) and 10% aq. $NaHCO_3$ (150 ml). The $CHCl_3$ layer was washed with H_2O, evaporated to dryness *in vacuo* and applied on a column of silica gel (80 g). Elution was carried out successively with $CHCl_3$–hexane (5: 2, v/v) (IVb and VIb), $CHCl_3$ (VIIb) and $CHCl_3$–MeOH (20: 1, v/v) (VIIIb). The separation of IVb and VIb was not complete and fractions which gave a single UV spot on TLC were collected. Compound IVb (630 mg, 43%) was recrystallized from MeOH to afford colorless needles. Compound VIb (70 mg, 6%) was dissolved in $CHCl_3$ and the dropwise addition of hexane afforded colorless needles, mp 154°; UV λ_{max}^{EtOH} nm: 232, 269, 291 (Fig. 1). *Anal.* Calcd. for $C_{10}H_{14}O_2N_4S$: C, 47.2; H, 5.51; N, 22.00; S, 12.60. Found: C, 47.07; H, 5.54; N, 22.09; S, 12.23. NMR (d_6-DMSO) δ: 1.13, 1.22 (3H each, t, CH_3), 2.92 (3H, d, J=5 Hz, NCH_3), 3.64, 3.96 (2H each, q, CH_2), 8.3 (1H, d, J=5 Hz, NH). Compound VIIb (350 mg, 23%) was recrystallized from MeOH to afford colorless platelets. Compound VIIIb (70 mg, 5%) was dissolved in EtOAc, and the dropwise addition of hexane afforded pale-yellow prisms, mp 128—130°; UV λ_{max}^{EtOH} nm: 251, 280, 315 (Fig. 2). *Anal.* Calcd. for $C_{12}H_{18}O_3N_4$: C, 54.12; H, 6.81; N, 21.04. Found: C, 54.01; H, 6.77; N, 21.11. NMR ($CDCl_3$) δ: 1.23 [6H, t, $(CH_3)_2$], 3.18, 3.25 (3H each, s, NCH_3), 4.03, 4.15 (2H each, q, CH_2), 7.73 (1H, s, CH), 9.83 (1H, s, CHO). B) The same mixture as above was refluxed for 16.5 hr. The product was chromatographed as described above to afford following fractions: IVb (440 mg, 30%), VIb (210 mg, 15%), VIIb (300 mg, 20%), VIIIb (40 mg, 3%). C) To an ice-cooled mixture of CH_2Cl_2 (125 ml) and $SOCl_2$ (70 ml) was added DMF (4.22 ml, 54.6 mmoles). After 15 min at 0°, Ib (10 g, 54.6 mmoles) was added and the mixture refluxed for 5.5 hr. The solution was evaporated to dryness *in vacuo* and the residue shaken with $CHCl_3$ (200 ml) and 7% aq. $NaHCO_3$ (300 ml). The $CHCl_3$ layer was washed twice with H_2O and evaporated to dryness *in vacuo*. The residue was recrystallized twice from MeOH to afford IVb as colorless needles (4.4 g, 30%), mp 87—89°.

6-Amino-1,3-diethyl-5-methyluracil (IX)——To a solution of IVb (1.07 g, 4 mmoles) in BuOH (50 ml) was added Raney Ni (5 ml, previously washed well with BuOH[13]) and the mixture refluxed for 3 hr under vigorous stirring. The Ni was filtered off from the mixture and the filtrate evaporated to dryness *in vacuo*. The residue was applied on a column of silica gel (50 g) and the column eluted with $CHCl_3$-MeOH (50: 1, v/v). Fractions which gave a single UV spot on TLC were pooled and evaporated to dryness *in vacuo* to afford colorless crystals (680 mg, 86%). They were dissolved in $CHCl_3$ and the dropwise addition of ether afforded colorless needles (440 mg), mp 155—157°; UV λ_{max}^{EtOH} nm: 277. *Anal.* Calcd. for $C_9H_{15}O_2N_3$: C, 54.80; H, 7.67; N, N, 21.28. Found: C, 54.90; H, 7.70; N, 21.33. NMR ($CDCl_3$) δ: 1.20, 1.30 (3H each, t, CH_3), 1.90 (3H, s, CH_3). 4.03 [4H, q, $(CH_2)_2$], 4.70 (2H, NH_2).

Methylation of 5,7-Diethyl-3-methylaminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H, 7H)-dione (VIb)——To a solution of VIb (0.5 g) in DMF (10 ml) were added K_2CO_3 (0.5 g) and MeI (0.5 ml) and the mixture was stirred at room temperature for 16 hr. The mixture was poured into $CHCl_3$ (50 ml), washed twice with H_2O, and the $CHCl_3$ layer was evaporated to dryness *in vacuo*. The residual syrup was dissolved in hexane (30 ml) and cooled to afford colorless needles (0.4 g, 80%), mp 90—91°; UV λ_{max}^{EtOH} nm: 235, 278, 308 (authentic IVb, mp 88—90°; UV λ_{max}^{EtOH} nm: 235, 278, 308).

1,3-Diethyl-6-(dimethylaminomethylene)aminouracil (XI)——To a solution of VIIb (0.5 g) in AcOH (15 ml) was added Zn powder (1 g) and the mixture refluxed for 2 hr under vigorous stirring. The Zn was filtered off from the mixture and the filtrate evaporated to dryness *in vacuo*. The residue was applied on a column of silica gel (30 g) and the column eluted with $CHCl_3$. Fractions which gave a single UV spot on TLC were pooled and evaporated to dryness *in vacuo* to give XI as colorless crystals (280 mg, 64%). They were dissolved in $CHCl_3$ and the dropwise addition of ether afforded colorless needles (180 mg), mp 137—138°; UV λ_{max}^{EtOH} nm: 248, 305 (Fig. 2). *Anal.* Calcd. for $C_{11}H_{18}O_2N_4$: C, 55.45; H, 7.62; N, 23.50. Found: C, 55.53; H, 7.71; N, 23.89. NMR (d_6-DMSO) δ: 1.05, 1.08 (3H each, t, CH_3), 2.98, 3.08 (3H each, s, NCH_3), 3.77, 3.96 (2H each, q, CH_2), 5.07 (1H, s, 5-H), 8.03 (1H, s, CH). Compound XI (190 mg) was dissolved in a mixture of EtOH and conc. NH_4OH (10 ml each) and left standing at room temperature for 16 hr. TLC of the resulting solution revealed a single UV spot having the same *Rf* value as that of Ib. Evaporation of the solution and recrystallization of the residue from 20% MeOH afforded colorless needles (80 mg), mp 198—200°; UV $\lambda_{max}^{H_2O}$ nm: 269 (authentic Ib, mp 198—199°; UV $\lambda_{max}^{H_2O}$ nm: 269).

N,O,O′-Triformyldiethanolamine——A mixture of diethanolamine (40 g, 0.4 mole), 99% HCOOH (128 g, 2.8 moles) and benzene (100 ml) was refluxed for 10 hr in a flask equipped with water-separator.[14] Benzene was removed *in vacuo* from the mixture and the residue distilled to afford colorless liquid (61.5 g, 85%), bp 155—160° (4 mmHg); NMR ($CDCl_3$) δ: 3.65, 4.33 (4H each, t), 8.03 (3H, s, CHO).

5,7-Diethyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidin-4(5H)-one-6(7H)-thione (IVj)——To an ice-cooled mixture of CH_2Cl_2 (23 ml) and $SOCl_2$ (13 ml) was added DMF (0.8 ml, 10.3 mmoles). After 15 min

13) When H_2O was not removed completely from the catalyst, IIIb was obtained as well as IX. This fact suggests the formation of IIb as the intermediate of this desulfurization.

14) L.F. Fieser and J.E. Jones, *Org. Synth.*, **20**, 66 (1940).

at 0°, Ij (2 g, 10 mmoles) was added and the mixture refluxed for 4 hr. The solution was evaporated to dryness *in vacuo* and the residue shaken with $CHCl_3$ (50 ml) and 10% aq. $NaHCO_3$ (100 ml). The $CHCl_3$ layer was washed with H_2O, evaporated to dryness *in vacuo* and applied on a column of silica gel (80 g). The column was eluted with $CHCl_3$ to afford three fractions. Fraction 1 was evaporated to dryness *in vacuo* to afford IVj as colorless needles (200 mg, 7%), which were recrystallized from EtOH, mp 163—168°; UV λ_{max}^{EtOH} nm (ε): 274 (13.8×10^3), 308 (33.0×10^3). *Anal.* Calcd. for $C_{11}H_{16}ON_4S_2$: C, 46.45; H, 5.68; N, 19.68; S, 22.54. Found: C, 46.43; H, 5.69; N, 19.48; S, 23.04. NMR ($CDCl_3$) δ: 1.1—1.55 [6H, m, $(CH_3)_2$], 3.36 [6H, s, N-$(CH_3)_2$], 4.3—5.0 [4H, m, $(CH_2)_2$]. Fraction 2 was evaporated to dryness *in vacuo* to afford IVb as colorless crystals (1.3 g, 49%), mp 89—90°; UV λ_{max}^{EtOH} nm: 236, 278, 308. Fraction 3 was evaporated to dryness *in vacuo* to afford red-brown syrup (140 mg), which revealed two UV spots on TLC and further purification of the syrup was not tried.

6-Amino-1-benzyl-4-thiouracil (XIII)——To a boiled solution of P_2S_5 (38 g, 170 mmoles) in pyridine (700 ml) were added Ik (20 g, 92 mmoles) and H_2O (1 ml)[15] and the mixture stirred for 5 hr at 125—130° (bath temp.). The solution was concentrated to *ca.* 100 ml and poured into ice-water (600 ml) under vigorous stirring. After having been neutralized with K_2CO_3, the solution was left standing at room temperature overnight to deposit a yellow-brown precipitate (11 g, 52%). UV λ_{max}^{EtOH} nm: 247, 327. $\lambda_{max}^{pH\ 11}$ nm: 271, 315.

6-Amino-1-benzyl-4-methylthiouracil (XIV)——To a suspension of XIII (11 g) in 50% MeOH (500 ml) were added 1 N NaOH (70 ml) and MeI (3 ml) and the mixture was stirred at room temperature for 10 min. After having been neutralized with 1 N HCl, the solution was concentrated to *ca.* 200 ml to deposit a precipitate, which was recrystallized from MeOH to afford pale-yellow platelets (6.7 g, 60%), mp 232—233° (decomp.); UV λ_{max}^{MeOH} nm: 232, 253, 304. *Anal.* Calcd. for $C_{12}H_{13}ON_3S$: C, 58.28; H, 5.30; N, 16.99; S, 12.97. Found: C, 57.72; H, 5.22; N, 16.64; S, 13.00.

6-Amino-1-benzylcytosine (XV)——The suspension of XIV (6.7 g) in 20% NH_3–MeOH (125 ml) was heated in a sealed tube at 170—175° (bath temp.) for 40 hr. The mixture was evaporated to dryness *in vacuo* and the residue recrystallized twice from MeOH to afford pale-yellow needles (3.63 g, 62%). This sample was used for the next reaction although it contained a small amount of impurities (TLC). For analyses, a part of this sample was recrystallized twice from MeOH to afford colorless needles, mp 260—265° (decomp.); UV λ_{max}^{EtOH} nm: 278. *Anal.* Calcd. for $C_{11}H_{12}ON_4$: C, 61.09; H, 5.60; N, 25.92. Found: C, 59.69; H, 5.11; N, 25.45.

4-Amino-7-benzyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidin-6(7H)-one (XVI)——To an ice-cooled mixture of 1,2-dichloroethane (120 ml) and $SOCl_2$ (20 ml) was added DMF (1.05 g, 14.4 mmoles). After 15 min at 0°, XV (3 g, 13.9 mmoles) was added and the mixture refluxed for 2 hr. Since XV did not dissolve in the mixture, 1,2-dichloroethane and $CHCl_3$ (30 ml each) were added and refluxing was continued for further 4 hr. The mixture was worked up similarly as in the case of IVb and applied on a column of silica gel (100 g), which was eluted with 1.5% MeOH–$CHCl_3$ to afford two fractions. Fraction 1 (230 mg, revealed three UV spots on TLC) was discarded. Fraction 2 (colorless powder, 2.38 g, revealed two UV spots on TLC) was dissolved in MeOH (30 ml) and kept in a refrigerator to afford XVI as pale-yellow needles (1.18 g, 28%). For analyses, a part of this sample was recrystallized twice from MeOH to afford colorless needles, mp 195—200°; UV λ_{max}^{EtOH} nm: 262, 299 (Fig. 1). λ_{max}^{EtOH,H^+} nm[16]: 296, 339. *Anal.* Calcd. for $C_{14}H_{15}ON_5S$: C, 55.79; H, 5.02; N, 23.24; S, 10.64. Found: C, 55.18; H, 5.25; N, 22.82; S, 10.40. NMR (d_6-DMSO) δ: 2.98 [6H, s, $(CH_3)_2$], 5.04 (2H, s, CH_2), 7.22 (5H, s, C_6H_5), 6.9—7.4 (2H, NH_2). The mother liquor, obtained by separating the crystals of XVI, was chromatographed again on silica gel (70 g) using the same elution solvent as above to afford three fractions. Fraction 1 (150 mg, revealed three UV spots) was discarded. Fraction 2 (200 mg) was identified as XVI on the basis of its mp and UV spectrum. Fraction 3 (380 mg, 9%) was recrystallized from MeOH to afford XVII as colorless plates (170 mg), mp 220—223°; UV λ_{max}^{EtOH} nm: 311 (Fig. 2). *Anal.* Calcd. for $C_{14}H_{16}ON_5Cl$: C, 55.01; H, 5.28; N, 22.90; Cl, 11.58. Found: C, 55.01; H, 5.18; N, 22.87; Cl, 11.68. NMR ($CDCl_3$) δ: 3.05 [s, 6H, $(CH_3)_2$], 5.22 (2H, s, CH_2), 6.1—6.5 (2H, NH_2), 7.3 (5H, s, C_6H_5), 7.54(1H, s, CH).

7-Benzyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H, 7H)-dione (IVl)——To an ice-cooled solution of XVI (50 mg) in AcOH–H_2O (1: 5, v/v, 6 ml) was added dropwise aq. $NaNO_2$ (0.8 g in 2 ml) and the mixture stirred at 0° for 2 hr and then at room temperature for 3 hr. The mixture was diluted with H_2O (10 ml) and extracted twice with $CHCl_3$ (10 ml). After having been washed with H_2O, the $CHCl_3$ layer was evaporated to dryness *in vacuo*, and the residue recrystallized from EtOH to afford colorless needles (40 mg, 80%), mp 244—245°; UV λ_{max}^{EtOH} nm: 233, 277, 306 (Fig. 1). *Anal.* Calcd. for $C_{14}H_{14}O_2N_4S$: C, 55.62; H, 4.67; N, 18.52; S, 10.60. Found: C, 55.39; H, 4.56; N, 18.87; S, 10.34. NMR (d_6-DMSO) δ: 3.25 [6H, s, $(CH_3)_2$], 5.08 (2H, s, CH_2), 7.26 (5H, s, C_6H_5), 11.0 (1H, NH).

1-Benzyl-5-chloro-6-(dimethylaminomethylene)aminouracil (VIII)——Compound XVII (50 mg) was deaminated in the same manner as described above and the product was recrystallized from MeOH to afford colorless plates (40 mg, 80%), mp 246—247°; UV $\lambda_{max}^{EtOH,H+16)}$ nm: 235, 257 (s), 310. $\lambda_{max}^{EtOH,OH-16)}$ nm: 229, 250 (s),

15) J.J. Fox, D.V. Praag, I. Wempen, I.L. Doerr, L. Cheong, J.E. Knoll, M.L. Eidinoff, and G.B. Brown, *J. Am. Chem. Soc.*, **81**, 178 (1959).

16) EtOH, H^+=1 N HCl–EtOH (1: 99); EtOH, OH^-=1 N NaOH–EtOH (1: 99).

298. *Anal.* Calcd. for $C_{14}H_{15}O_2N_4Cl$: C, 54.85; H, 4.93; N, 18.27; Cl, 11.56. Found: C, 54.88; H, 4.77; N, 18.20; Cl, 11.60.

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